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PARIS, le 1 December 1952

Dear Josh,

The delay in answering your letter has been due to the alternating illnesses of Jacques and myself. We haven't really been able to get together to discuss in detail the program of Pz distribution in various mutants, a program which we have more or less abandoned because of the necessity of preparing a whole series of mutants. But your kindness in offering them to us makes me pick up my radar-like ears, and start thinking again (presumably with my ears). Naturally, we are interested in those mutants; in fact, we'd love to have them. I must admit to you that, for our isotope program I have absorbed only sera left, so that there will be a delay in my setting up titrations for Pz. I will, however, be preparing a new lactase batch, and immunizing rabbits, at which time I will be able to do some titrations.

Our best evidence is that Pz is involved in the utilisation of galactose; it might be either galactokinase or waldenase. The reason for this hunch is that, in certain lactose-negative strains, which are also galactose-negative, α-galactosides, including galactose itself, induce the formation of Pz. These strains could be considered to be galactose-negative either because they lack kinase or waldenase; I suspect it's the latter.

I would therefore like as many different galactose-negative strains as you have, especially constitutive and glucose-negative ones. The following is a list of the kind of mutants I would like: 1) all glucose-negative mutants deficient at various points (if known) in the glycolytic or oxidative cycles; glucose-negative, lactose-positive,-constitutive, and galactose-positive or -negative. 2) as many different galactose-negative strains; here again constitutive, lactose-positive. 3) melibiose-negative, lactose-positive or -negative, and galactose-positive or -negative. 4) arabinose-negative and -positive, with galactose-negative and -positive. 5) lactose-negative series 1 to 7. This might be considered a tall order, and I only suggest such an ambitious program because I am training a new technician to do the immunochemical work.

We have all of the mutants you sent us. Since Jacques is not here at present, I have been unable to go through the complete stock of mutants of K12 which we have manufactured, but will send that on to you in another letter. I don't think that they will be of much interest to you, as they are probably on a small scale what you have done on a large scale. We have amylomaltase constitutive mutants of K12 and ML isolated by Jacque's technique of alternate passage through maltose and glucose.

Once I am here in a letter, I'd like to tell you a little bit about some of our recent work. We have been working on a phenomenon which we call specific inhibition. It may be looked at as the symmetrical corollary of specific induction. For example, we have found that cells grown in the presence of methionine or tryptophane lose the ability to synthesize these substances. We have shown that this loss of ability is due to the loss of specific enzyme involved in their synthesis. In the case of methionine, it's the enzyme which converts homocystine to methionine, and in the case of tryptophane, it is the desmolase which couples indol and serine. The phenomenon of the products of an enzyme-reaction inhibiting the induction of that

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enzyme is not unknown, and we have found that the inducers of the adaptive galactosidase inhibit the synthesis of the constitutive enzyme, for example galactose. This is also true for the constitutive β-glucosidase of yeast. In a way, this mechanism is very satisfying intellectually, as the cell which, in the presence of an essential metabolite, ceases to synthesize the enzyme leading to the formation of this metabolite, is at maximum efficiency. Another interest in the system is that we are now able to convert any constitutive enzyme into an adaptive one, and in fact, have begun to study tryptophane desmolase, classically constitutive, as an adaptive enzyme.

Dave Hogness from Beadle's laboratory, with us now, has taken up the study of the specificity of induction, and has begun to investigate the mechanism of the neolactose effect, and the metabolism of induction. It seems that the neolactose does not induce because it does not undergo the proper metabolism. Altrose itself does not inhibit induction, nor do altrose derivatives. Hogness has begun to study the specificity of melibiase formation, which proves to be a system as interesting as β-galactosidase, and even less complicated.

Martin Pollock has been trying to dissect the mechanism of enzyme induction using ultra-violet, and in his penicillinase system, finds that, whereas the primary interaction of penicillin to organizer ~~is not touched~~ IS NOT TOUCHED, and the active phase where penicillinase is synthesized linearly, the latent period between these two steps is tremendously prolonged. Its interpretation remains to be seen.

I have finally reached the end of a by-product study on the inhibition of induction by glucose (diauxie). It is certainly not due to interaction of proteins, and in fact, outside of Pz and Gz, I don't believe any other system is clear. The glucose acts to inhibit both the penetration into and out of the cell, of the inducer.

We will be doing our isotope experiments soon, and hope to obtain some cleancut results on the precursors. I've developed a general technique for determining the absolute purity of any adaptive enzyme, and hope to illustrate it with the β-galactosidase.

We cannot thank you enough for your kind offer of your strains. They will be of immeasurable aid to Jacques and me, as we don't seem to be able to do alone everything we'd like to.

Incidentally, it is just about decided that I'll be returning to the States in September, '54, although I don't have a job lined up yet. Any chance of seeing you over here before then? With best regards,

Sincerely yours,
Mel